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ORIGINAL REPORT

Trastuzumab-Related Cardiotoxicity Among Older Patients With Breast Cancer

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ABSTRACT

Purpose
The use of trastuzumab in the adjuvant setting improves outcomes but is associated with cardiotoxicity manifested as congestive heart failure (CHF). The rates and risk factors associated with trastuzumab-related CHF among older patients are unknown.

Patients and Methods
Breast cancer patients at least 66 years old with full Medicare coverage, diagnosed with stage I-III breast cancer between 2005 and 2009, and treated with chemotherapy were identified in the SEER-Medicare and in the Texas Cancer Registry–Medicare databases. The rates and risk factors associated with CHF were evaluated. Chemotherapy, trastuzumab use, comorbidities, and CHF were identified using International Classification of Diseases, version 9, and Healthcare Common Procedure Coding System codes. Analyses included descriptive statistics and Cox proportional hazards models.

Results
In total, 9,535 patients were included, of whom 2,203 (23.1%) received trastuzumab. Median age of the entire cohort was 71 years old. Among trastuzumab users, the rate of CHF was 29.4% compared with 18.9% in nontrastuzumab users ($P < .001$). Trastuzumab users were more likely to develop CHF than nontrastuzumab users (hazard ratio [HR], 1.95; 95% CI, 1.75 to 2.17). Among trastuzumab-treated patients, older age (age > 80 years; HR, 1.53; 95% CI, 1.16 to 2.10), coronary artery disease (HR, 1.82; 95% CI, 1.34 to 2.48), hypertension (HR, 1.24; 95% CI, 1.02 to 1.50), and weekly trastuzumab administration (HR, 1.33; 95% CI, 1.05 to 1.68) increased the risk of CHF.

Conclusion
In this large cohort of older breast cancer patients, the rates of trastuzumb-related CHF are higher than those reported in clinical trials. Among patients treated with trastuzumab, those with cardiac comorbidities and older age may be at higher risk. Further studies need to confirm the role that the frequency of administration plays in the development of trastuzumab-related CHF.

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INTRODUCTION

Approximately 25% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2) –*neu*.[1] Trastuzumab, a humanized monoclonal antibody against the extracellular domain of HER2, is a pivotal component in the treatment of patients with HER2-overexpressed or -amplified tumors. Trastuzumab improves outcomes when given with adjuvant chemotherapy,[2-8] but its use is associated with an increased risk of cardiotoxicity, which is attributed to blocking HER2 signaling in cardiac myocytes.[9] The overall incidence of trastuzumab-related cardiotoxicity varies according to the definition used, but it ranges from 2% to 7% for trastuzumab monotherapy, 2% to 13% for trastuzumab combined with paclitaxel, and can be as high as 27% when used in combination with anthracyclines.[4,10-16] In the pivotal adjuvant clinical trials, the rates of symptomatic congestive heart failure (CHF) ranged from 1.5% to 5.1%, and the rates of decreased left ventricular ejection fraction (LVEF) ranged from to 3.5% to 19%.[2,4,6,7,11,17-20]

Recent reports suggest that the incidence of trastuzumab-related cardiotoxicity is higher outside clinical trials,[21-23] and that older patients are at higher risk.[23-26] Of particular concern is cardiotoxicity in older women; data from National Surgical Adjuvant Breast and Bowel Project study B31/N9831 indicate that age is a risk factor for trastuzumab-related CHF.[18,27] The mean age of the patients included in the pivotal adjuvant trials was 51 to 52 years old and, in most studies, patients 70 years and older were excluded.[7] The American Cancer Society estimates that 45% of

breast cancer patients are older than 65 years[28]; therefore, it is important to quantify the risk of trastuzumab-related cardiotoxicity in this population.

PATIENTS AND METHODS

Data Source

We used the SEER-Medicare and the Texas Cancer Registry (TCR) –Medicare linked databases for this study. The SEER program, supported by the US National Cancer Institute (NCI), collects data from tumor registries, covering 25% of the population of the United States.[29] The Medicare program is administered by the Centers for Medicare & Medicaid Services and covers 97% of the US population ages 65 years and older.[30] SEER participants are matched with their Medicare records under an agreement between the NCI and the Centers for Medicare & Medicaid Services. Of SEER participants who were diagnosed with cancer at age 65 years or older, 94% are matched with their Medicare enrollment records.[30]

The TCR is a component of the Texas Department of State Health Services and is the fourth largest statewide population-based registry in the United States, with 240,000 reports of cancer annually. TCR is not part of SEER, but it collects data according to standardized registry rules and is Gold Certified by the North American Association of Central Cancer Registries. The NCI linked the TCR database with Texas Medicare data using a probabilistic linkage method, with the same methodology as the SEER-Medicare linkage.[31]

Study Population

We included patients at least 66 years old who were diagnosed with invasive breast cancer stages I-III between 2005 and 2009 (for SEER-TCR participants information was only available from 2005 to 2007). All patients were treated with chemotherapy started within the first 6 months after diagnosis, as a way to identify patients treated in the adjuvant setting. Patients were required to have Medicare Parts A and B and were not to be members of a health maintenance organization (HMO) for 1 year before and after their breast cancer diagnosis to identify comorbidities, because Medicare claims are not complete for HMO members. Patients with a previous history of CHF, cancer, or noncarcinoma histology were excluded.

We identified 82,751 patients 66 years old and older diagnosed with nonmetastatic invasive breast cancer between 2005 and 2009. Of them, 55,581 had full coverage of Medicare Parts A and B and were not members of an HMO. There was no difference in the stage distribution between patients according to Medicare/HMO coverage; however, patients with full coverage were older (median, 76 *v* 74 years). Among the 55,581 eligible patients, 10,828 received treatment with chemotherapy within the first 6 months of diagnosis. After excluding patients with previous history of CHF or cancer, the final study population included 9,535 patients (7,937 from SEER-Medicare and 1,598 from TCR-Medicare).

Data Extraction and Definitions

Administrative codes are a reliable method to identify cardiac conditions; high specificity and high positive predictive value have been previously reported.[32-34] CHF after breast cancer diagnosis was identified using the following International Classification of Diseases version 9 (ICD-09) diagnosis codes in inpatient, durable medical equipment, physician, and outpatient files: 425, 428, and 785.51. To increase specificity, patients were considered to have CHF if there was at least one claim in the inpatient file or at least two claims that were more than 30 days apart for outpatient files. Comorbid conditions from 12 months to 1 month before the diagnosis of breast cancer were identified in the Medicare inpatient, outpatient, and physician claims data. A comorbidity score was calculated using Klabunde's adaptation of the Charlson comorbidity index.[5,35,36] Cardiac-specific comorbidities were identified with the following ICD-09 codes: hypertension (401-409, exclude 402.11, 402.91), coronary artery disease (CAD; 410-414, exclude 414.1, 36.0, 36.1), valve disorders (394-397, 424, exclude 424.9, 35), hyperthyroidism (242.9), diabetes (250), and emphysema (492). Using Healthcare Common Procedure Coding System (HCPS) codes we identified the use of trastuzumab (J9355) anthracyclines (J9000, J9010, J9001, J9180, J9178), and taxanes (J9265, J9170, J9171, J9264).

Patients received follow-up from diagnosis date until loss of Medicare coverage, enrollment in HMO, or death. Date of last follow-up was December 31, 2010.

Statistical Analysis

Demographic and tumor characteristics of patients treated with and not treated with trastuzumab were compared using the χ^2 test or Wilcoxon's test. Using the Kaplan-Meier method, time-to-event rates were calculated starting from the date of breast cancer diagnosis to the first CHF claim or censoring time. Stratification according to trastuzumab and anthracycline use was performed; comparisons were made using the log-rank test.

A Cox regressions model using trastuzumab as a time-dependent variable was used to calculate the hazards of CHF for trastuzumab-treated patients compared with nontrastuzumab-treated patients. Variables in the model included age, sex, race/ethnicity, year of diagnosis, SEER-region (TCR was included as a region), stage, tumor grade, surgery, radiation, anthracycline use, taxane use, estrogen receptor, progesterone receptor, history of hypertension, and Charlson comorbidity score. Results are expressed using hazard ratios (HR) and 95% CI. As a proxy for severity, we built the same model using only codes for CHF identified in the inpatient file. We evaluated interaction terms to test the proportional hazards assumption. Stratification analysis showed that the resulting HR under all this analysis was almost the same, proving that the introduction of time-dependent variables did not violate the assumptions of the model. A sensitivity analysis using a competing risk-regression model was performed.

To determine the risk factors associated with CHF among trastuzumab-treated patients, a Cox regression model was used including only the trastuzumab-treated patients who were CHF-free at the time the first dose of trastuzumab was administered (n = 2,047). Variables included frequency of trastuzumab administration, CAD, valve disorders, hyperthyroidism, diabetes, and emphysema, in addition to those previously mentioned with the exception of Charlson comorbidity score.

All computer programming and statistical analyses were performed with the SAS system (Cary, NC). All tests were two-sided. The institutional review board of The University of Texas MD Anderson Cancer Center approved this study by granting an exemption in the absence of informed consent.

RESULTS

A total of 9,535 patients were included. Median age of the cohort was 71 years old. We identified 2,203 trastuzumab-treated patients (23.1%). No differences in the Charlson comorbidity score existed between trastuzumab-treated and nontrastuzumab-treated patients. Patients treated with trastuzumab were less likely to receive anthracyclines and were more likely to be treated with taxanes ($P < .001$). Patient characteristics are listed in Table 1.

Among trastuzumab users, the rate of CHF was 29.4% compared with 18.9% in nontrastuzumab users ($P < .001$). Figure 1 illustrates the Kaplan-Meier curve for time-to-CHF according to trastuzumab use and trastuzumab stratified by anthracycline use.

After adjusting for potential confounders, trastuzumab users were more likely to develop CHF than nontrastuzumab users (HR, 1.95; 95% CI, 1.75 to 2.17). Similar results were seen when competing risk regression was used (data not shown). Using 66 to 70 years old as the reference category, patients in the 76- to 80-year-old group had a higher risk (HR, 1.43; 95% CI, 1.26 to 1.61), and those patients older than 80 years were at the highest risk of CHF (HR, 1.76; 95% CI, 1.48 to 2.09). Other variables associated with increased risk of CHF included race (HR, 1.22; 95% CI, 1.05 to 1.43 for non-Hispanic black patients *v* white patients), comorbidities (HR, 1.32; 95% CI, 1.18 to 1.46; and HR, 1.74; 95% CI, 1.50 to 2.02, for Charlson scores of 1 and ≥ 2, respectively), hypertension (HR, 1.29; 95% CI, 1.18 to 1.42),

Table 1. Patient Characteristics According to Trastuzumab Use (N = 9,535)

Demographics	All Chemotherapy Patients (%; N = 9,535) No. of Patients	%	Percent of Trastuzumab Users (n = 2,203)	Percent of Non-Trastuzumab Users (n = 7,332)	*P*
Year of diagnosis					
2005	2,142	22.5	19.8	23.3	.004
2006	2,128	22.3	22.7	22.2	
2007	2,159	22.6	23.2	22.5	
2008	1,583	16.6	16.5	16.6	
2009	1,523	15.9	17.8	15.4	
Age, years					
66-70	4,674	49.0	43.9	50.6	< .001
71-75	2,837	29.8	29.7	29.8	
76-80	1,420	14.9	16.4	14.4	
> 80	604	6.3	9.9	5.25	
Race/ethnicity					
Hispanic	766	8.0	8.6	7.86	.004
NH black	771	8.1	6.3	8.62	
NH other	422	4.4	4.7	4.35	
NH white	7,576	79.5	80.4	79.2	
Sex					
Female	9,419	98.8	99.4	98.6	.005
Male	116	1.2	0.6	1.4	
ER status					
Negative	2,632	27.6	36.8	24.8	< .001
Positive	4,907	51.46	42.1	54.3	
Unknown	1,996	20.93	21.1	20.9	
PR status					
Negative	3,647	38.3	49.7	34.8	< .001
Positive	3,844	40.3	28.6	43.8	
Unknown	2,044	21.4	21.7	21.4	
Stage					
Localized	3,910	41.0	47.1	39.2	< .001
Regional	5,625	58.9	52.9	60.8	
Radiation					
No	5,067	53.1	57.3	51.9	< .001
Yes	4,071	42.7	38.6	43.9	
Unknown	397	4.2	4.1	4.2	
Charlson comorbidity scale					
0	6,846	71.8	72.2	71.7	.144
1	2,038	21.4	20.3	21.7	
≥ 2	651	6.84	7.5	6.6	
Anthracycline use					
0	4,306	45.2	60.6	40.5	< .001
1-4	4,438	46.5	35.9	49.7	
≥ 5	791	8.3	3.5	9.7	
Taxane use					
No	2,496	26.2	20.8	27.8	< .001
Yes	7,039	73.8	79.2	72.2	
CAD					
No	8,887	93.2	93.6	93.1	.400
Yes	648	6.8	6.4	6.9	
Hypertension					
No	4,758	49.9	50.3	49.8	.638
Yes	4,777	50.1	49.7	50.2	
Valve disease					
No	9,311	97.6	97.5	97.7	.603
Yes	224	2.34	2.5	2.3	
Diabetes					
No	7,803	81.8	82.2	81.7	.607
Yes	1,732	18.2	17.8	18.3	

NOTE. Included patients were diagnosed with stage I-III breast cancer between 2005-2009, were older than ≥ 66 years, and were treated with adjuvant chemotherapy.

Abbreviations: CAD, coronary artery disease; ER, estrogen receptor; NH, non-Hispanic; PR, progesterone receptor.

and anthracycline use (one to four cycles: HR, 1.33; 95% CI, 1.20 to 1.48; ≥ five cycles: HR, 1.50; 95% CI, 1.27 to 1.77). Table 2 shows the complete model. When evaluating only inpatient claims for CHF, trastuzumab-treated patients were also at increased risk (HR, 1.20; 95% CI, 1.00 to 1.43; $P = .049$).

Among trastuzumab-treated patients older than 80 years (HR, 1.53; 95% CI, 1.12 to 2.01), cardiac comorbidities such as CAD (HR, 1.82; 95% CI, 1.34 to 2.48) and hypertension (HR, 1.24; 95% CI, 1.02 to 1.50) were associated with increased risk of CHF. Using administration of trastuzumb once every 3 weeks (21-day cycles) as a reference category, once-a-week administration was associated with an increased risk (HR, 1.33; 95% CI, 1.05 to 1.68). The complete model is shown in Table 3. Among trastuzumab-treated patients who developed CHF, 68.8% of the events occurred within the first 12 months after initiation of treatment.

DISCUSSION

CHF rates among older patients treated with trastuzumab are higher than the rates that have been reported among clinical trial participants. There is an absolute increase in the risk of CHF of 10% among trastuzumab-treated patients (29.4% *v* 18.9%). In this large cohort of older patients with breast cancer, the risk of CHF and CHF hospitalizations was 1.95 and 1.20 times higher among patients treated with trastuzumab than those who were not. We identified that older age and cardiac comorbidities are important factors associated with the risk of CHF among trastuzumab-treated patients.

In the general population, in which treated patients are older and have more comorbidities, the rates of CHF are expected to be higher than among clinical trial participants. In a study evaluating the long-term cardiac safety of trastuzumab, the rate of CHF or asymptomatic decrease in LVEF was 28%.[21] Similarly, the Canadian group in British Columbia reported that 21.6% of their patients treated in the adjuvant setting with sequential trastuzumab developed a cardiac event.[22] These estimates are dramatically different to what has been reported in the pivotal clinical trials. In the 7-year follow-up period of NSABP-B31, 4.0% of the patients who received trastuzumab experienced a cardiac event, compared with 1.3% among those in the control arm.[18] In the Breast Cancer International Research Group 006 study, the incidence of CHF was 2% among patients treated with doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab, 0.4% in patients treated with docetaxel, carboplatin and trastuzumab, and 0.7% in those treated with doxorubicin and cyclophosphamide followed by paclitaxel without trastuzumab. The rates of subclinical decrease in LVEF were 18.6%, 9.4%, and 11.2%, respectively.[7]

Our high-risk estimates are similar to recently published data. In a cohort of 490 Italian patients treated with trastuzumab in the adjuvant setting, the overall rate of trastuzumab-related CHF was 27%, but was 38% for patients older than 68 years.[26]

In a recently published study,[3] the rates of CHF among patients with breast cancer were evaluated using data from the Cancer Research Network. Among 12,500 women, 554 trastuzumab-treated patients were identified. The 5-year rates of CHF were 3.1% for patients not treated with chemotherapy, 4.3% for patients

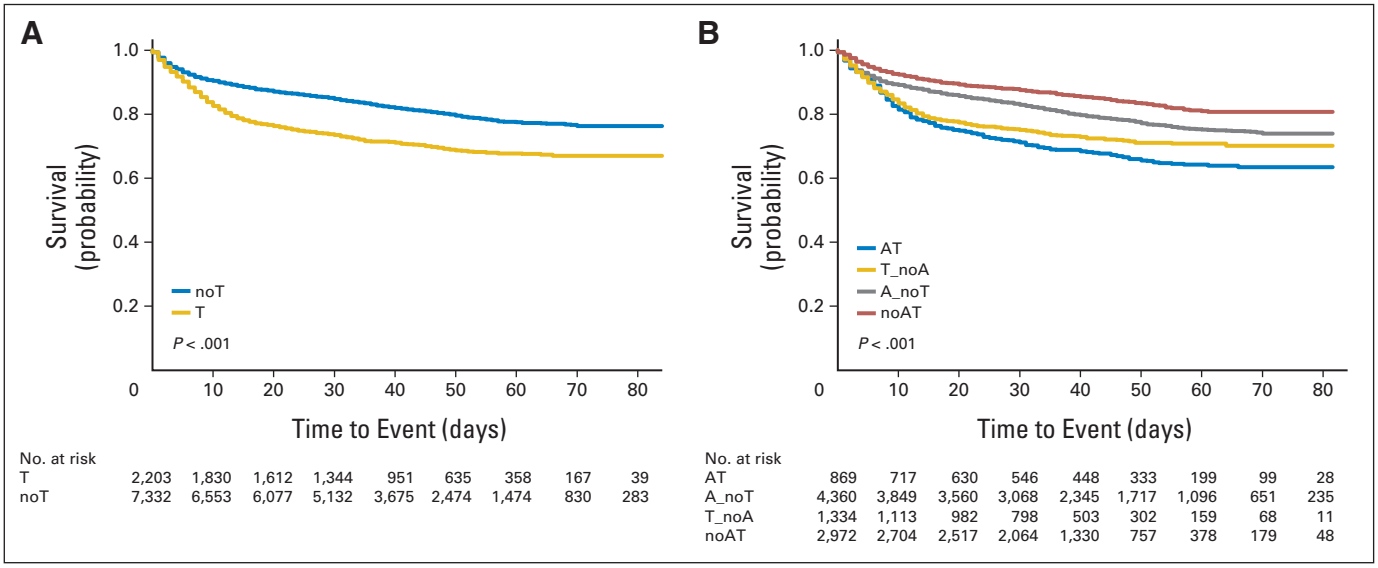

Fig 1. Congestive heart failure (CHF) –free survival for patients with breast cancer, time since breast cancer diagnosis to first CHF claim (in months). (A) According to trastuzumab use. (B) According to trastuzumab and anthracycline use. AT, anthracycline and trastuzumab; A_noT, anthracycline and no trastuzumab; T_noA, trastuzumab and no anthracycline; noAT, no anthracycline or trastuzumab.

treated with anthracyclines, 21.1% for those receiving trastuzumab, and 20.1% for patients receiving trastuzumab and anthracyclines. Despite the large patient population, only 4,910 of the patients were older than 65 years, of whom 1,704 patients were treated with chemotherapy and only 82 patients received trastuzumab. The authors observed higher rates of CHF according to age; the highest rates were seen among patients older than 75 years treated with trastuzumab and anthracyclines (n = 8).

In a population-based study evaluating an earlier time frame, before trastuzumab was incorporated as standard of care in the adjuvant setting, Du et al[25] reported the rates of cardiotoxicity among a heterogeneous population of patients with stage I-IV breast cancer (n = 880). Compared with patients not treated with chemotherapy, those who received trastuzumab in combination with an anthracycline (HR, 2.37; 95% CI, 1.76 to 3.19), trastuzumab alone (HR, 1.97; 95% CI, 1.46 to 2.67), or anthracyclines alone (HR, 1.19; 95% CI 1.05 to 1.34) were at higher risk of CHF. In contrast with this study, our study is exclusively focused on the risk associated with adjuvant therapy and therefore our results are not influenced by the increased risk of CHF among heavily pretreated patients with metastatic disease.

Chen et al[23] evaluated the rates of CHF using the SEER-Medicare database in a cohort that included 862 trastuzumab-treated patients in the adjuvant setting. Compared with patients not treated with chemotherapy, patients treated with anthracycline and trastuzumab had the highest risk of CHF (incidence rate ratio [IRR], 2.32; 95% CI, 1.87 to 2.87), followed by patients treated with trastuzumab (IRR, 1.78; 95% CI, 1.43 to 2.21) and patients treated with anthracyclines (IRR, 1.12; 95% CI 1.02 to 1.23). In our time-to-event analysis, we observed a similar pattern, suggesting that in this patient population the risk of CHF is higher with the use of trastuzumab-based chemotherapy than with the use anthracycline-based chemotherapy.

Some groups have reported that anthracycline use, higher body mass index, hypertension, antihypertensive therapy, and older age are risk factors for the development of trastuzumab-related CHF.[23,26,37-39] The updated analysis of NSABP-B31,[18] demonstrated that the use of antihypertensive medications (HR, 2.10; 95% CI, 1.07 to 4.13), baseline LVEF of 50% to 54% (HR, 6.72; 95% CI, 2.67 to 16.92), post–doxorubicin and cyclophosphamide LVEF of 50% to 54% (HR, 11.84; 95% CI, 3.90 to 35.99), and age (age 50 to 59 years: HR, 2.43; 95% CI, 1.14 to 5.19; age ≥ 60 years: HR, 2.73, 95% CI, 1.13 to 6.60) were associated with increased risk. Our study is unique as we included the largest patient population of older patients with breast cancer treated with adjuvant chemotherapy. Among the 2,047 trastuzumab-treated patients who were CHF-free at the time of the first trastuzumab dose, we identified characteristics associated with higher risk of CHF. The risk of CHF increased according to age, with patients older than 80 years being at the highest risk. Cardiac comorbidities CAD and hypertension were also associated with increased risk. Patients with valve disease and those treated with anthracyclines had a borderline significant increase in risk.

Our study makes the important and unique observation that the frequency of trastuzumab administration could be associated with CHF, with patients receiving once-a-week trastuzumab being at higher risk. In the trials that led to the approval of trastuzumab in the metastatic setting, trastuzumab was administered weekly.[15,16,40] Further studies demonstrated that a less frequent administration did not compromise efficacy of safety.[40,41] However, some pharmacokinetic differences exist between the once-a-week and the once-every-3-weeks administration. For example, the maximum serum concentration is higher using the weekly regimen and the mean trough concentrations are 20% lower at the end of the every-3-weeks administration, compared with the same time point using it weekly.[42] It is possible that the more frequent administration is associated with greater myocyte damage. In addition, this phenomenon could be specific to older patients, so our results cannot be extrapolated to a younger patient population. Our observations are provoking and hypothesis-generating but need to be interpreted with caution. Further studies are needed to confirm the role that the frequency of administration plays in the development of trastuzumab-related CHF.

Table 2. Cox Regression Model Using Trastuzumab As a Time-Dependent Variable Among Patients Diagnosed With Stage I-III Breast Cancer Between 2005-2009 Who Were Older Than ≥ 66 Years and Were Treated With Adjuvant Chemotherapy (N = 9,535)

Variable	Univariate Model		Multivariate Model*	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Herceptin				
No	Ref		Ref	
Yes	1.83	1.65 to 2.03	1.95	1.75 to 2.18
Age, years				
66-70	Ref		Ref	
71-75	1.13	1.02 to 1.25	1.08	0.98 to 1.21
76-80	1.48	1.31 to 1.67	1.43	1.26 to 1.62
> 80	1.86	1.59 to 2.18	1.78	1.48 to 2.09
Race/ethnicity				
White	Ref		Ref	
Hispanic	1.04	0.88 to 1.22	0.89	0.76 to 1.06
Black	1.30	1.12 to 1.50	1.22	1.05 to 1.43
Other	0.87	0.69 to 1.09	0.79	0.62 to 1.00
Year of diagnosis				
2005	Ref		Ref	
2006	0.87	0.77 to 0.97	0.85	0.75 to 0.95
2007	0.73	0.64 to 0.83	0.75	0.66 to 0.85
2008	0.64	0.56 to 0.74	0.70	0.60 to 0.82
2009	0.56	0.48 to 0.66	0.61	0.51 to 0.72
Stage				
Localized	Ref		Ref	
Regional	1.13	1.03 to 1.23	1.03	0.93-1.31
Charlson comorbidity scale				
0	Ref		Ref	
1	1.42	1.28 to 1.57	1.31	1.19 to 1.46
≥ 2	1.96	1.70 to 2.27	1.74	1.50 to 2.03
Anthracycline use				
0	Ref		Ref	
1-4 cycles	1.21	1.10 to 1.33	1.33	1.20 to 1.48
≥ 5 cycles	1.30	1.11 to 1.51	1.50	1.27 to 1.77
Taxane use				
No	Ref		Ref	
Yes	1.00	0.90 to 1.10	1.07	0.96 to 1.19
Hypertension				
No	Ref		Ref	
Yes	1.44	1.32 to 1.58	1.29	1.77 to 1.42

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; Ref, reference; TCR, Texas Cancer Registry.

*Variables in the model included those in the table and SEER region (TCR was included as a region), sex, tumor grade, ER status, PR status, surgery, and radiation therapy.

Table 3. Cox Proportional Hazards Model Evaluating Factors Associated With CHF Among Breast Cancer Patients Diagnosed With Stage I-III Breast Cancer Between 2005-2009 Who Were Treated With Trastuzumab-Based Adjuvant Chemotherapy (n = 2,047)

Variable	Univariate Model		Multivariate Model*	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Trastuzumab administration				
Every 3 weeks	Ref		Ref	
Every week	1.43	1.14 to 1.80	1.33	1.05 to 1.68
Every 2 weeks	0.96	0.77 to 1.19	0.98	0.78 to 1.24
Every 4 weeks or more	1.47	1.03 to 2.08	1.40	0.98 to 2.00
Age, years				
66-70	Ref		Ref	
71-75	1.09	0.88 to 1.36	1.04	0.83 to 1.30
76-80	1.25	0.97 to 1.61	1.20	0.92 to 1.56
> 80	1.67	1.26 to 2.21	1.53	1.12 to 2.10
Race/ethnicity				
White	Ref		Ref	
Hispanic	0.78	0.55 to 1.11	0.66	0.46 to 1.00
Black	0.95	0.64 to 1.39	0.95	0.64 to 1.42
Other	0.81	0.52 to 1.26	0.70	0.44 to 1.12
Anthracycline use, cycles				
0	Ref		Ref	
1-4	1.11	0.92 to 1.33	1.07	0.86 to 1.32
≥ 5	1.06	0.65 to 1.74	0.99	0.59 to 1.64
Taxane use				
No	Ref		Ref	
Yes	0.95	0.77 to 1.18	1.02	0.80 to 1.29
CAD				
No	Ref		Ref	
Yes	2.04	1.53 to 2.72	1.82	1.34 to 2.48
Valve disease				
No	Ref		Ref	
Yes	1.71	1.07 to 2.74	1.52	0.92 to 2.49
Hypertension				
No	Ref		Ref	
Yes	1.33	1.11 to 1.59	1.24	1.02 to 1.50
Diabetes				
No	Ref		Ref	
Yes	1.26	1.01 to 1.58	1.23	0.89 to 1.43
Emphysema				
No	Ref		Ref	
Yes	2.21	0.83 to 5.91	2.27	0.83 to 6.25

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; ER, estrogen receptor; PR, progesterone receptor; Ref, reference; TCR, Texas Cancer Registry.

*Variables in the model include those in the table and SEER region (TCR was included as a region), sex, tumor grade, ER status, PR status, stage, surgery, and radiation therapy.

A large proportion of patients with newly diagnosed breast cancer are 65 years or older. Patients in this age group have been consistently underrepresented in clinical trials and, therefore, the risk of toxicities of current treatments is not known in this patient population. It has been shown that older patients with breast cancer have more comorbidities and are less likely to be treated with chemotherapy than younger patients. In addition, if treated, they are less likely to receive treatment with cardiotoxic medications, specifically anthracyclines.[38,43,44] In addition to being the largest population-based study published to date evaluating the use of trastuzumab among older patients with breast cancer, our study is different from other population-based studies[23,25] because we evaluated only patients treated with chemotherapy, making it a more homogeneous group of patients. We believe this should be of particular interest for the clinician who has decided to treat a patient and who needs risk estimates that are easy to apply and interpret. Our study is also unique as we evaluated CHF hospitalization as a marker for severity. Trastuzumab-treated patients had a 1.95- and 1.2-fold increase of CHF and CHF hospitalizations, respectively. The difference in the magnitude of the estimates suggests that only a minority of the trastuzumab-CHF related events require hospitalizations, and that most of the events can be managed in the outpatient setting. This highlights the importance

of cardiac monitoring for early detection. In our cohort, 23.1% of the patients received trastuzumab-based chemotherapy, data on HER2 status was not available, but this percentage is consistent with the rates of HER2-positive breast cancer in the general population.[1,45] This indicates, that, regardless of their age, patients were offered a medication that has shown to improve outcomes despite the potential risk of cardiotoxicity.

In addition, combining the TCR-Medicare and SEER-Medicare databases is unique to our study, and it allowed us to identify an even larger cohort of patients. We acknowledge that our study is limited by its retrospective nature and the characteristics inherent to claims-based research. SEER-Medicare and TCR-Medicare do not allow for assessment of the severity of outcome—therefore the need to evaluate CHF hospitalizations as a proxy for severity—and no information about LVEF is available. In addition, we were not able to evaluate the impact CHF had in the performance status or quality of life of the patients. We were not able to include in the analysis data on antihypertensive medication use, smoking, or obesity, as these data were not available. Despite including in the multivariable models important demographic and clinical characteristics, residual confounding cannot be completely excluded as patients treated with trastuzumab were younger and treated with different chemotherapy regimens. We believe, however, that if any residual confounding exists, it will likely cause an underestimation of our results and it will not compromise the interpretation of the data. Despite its limitations, our study provides important real-world information that will be useful for clinicians when discussing the risks and benefits of breast cancer therapy among older patients with breast cancer. This population-based study included only patients 66 years or older, making our results applicable to a large proportion of patients with breast cancer. In conclusion, among older patients, the rates of CHF are higher than among younger and healthier patients with breast cancer, and as physicians we should be aware of such increased risk so CHF can be identified and treated in a timely manner. It is possible that among high-risk patients, early cardiology referral, the use of prophylactic cardioprotective agents, and close monitoring may be beneficial.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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